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Convergent synthesis of an HIJK ring model of ciguatoxin via Suzuki cross-coupling reaction

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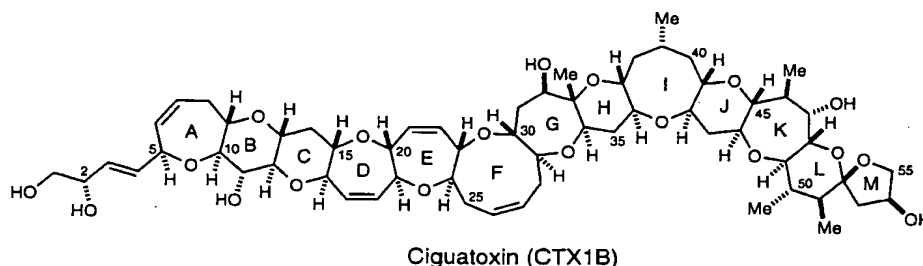
Abstract

Convergent synthesis of HIJK ring model compound **1** of ciguatoxin is described. The present synthesis relied on a palladium-catalyzed Suzuki cross-coupling reaction between eight-membered ketene acetal phosphate **2** and seven-membered alkylborane **6**. © 2000 Elsevier Science Ltd. All rights reserved.

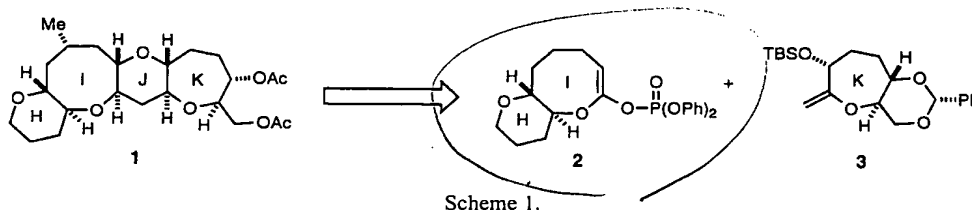
Keywords: coupling reactions; polyethers; Suzuki reactions; toxins.

Marine polycyclic ethers, such as brevetoxins, ciguatoxins, and maitotoxin, present formidable and challenging synthetic targets due to their structural complexity and exceptionally potent biological activities.¹ One most critical issue in the synthesis of these large natural products is the development of synthetic methodology for convergent coupling of polyether fragments.^{2,3} In connection with our synthetic studies on ciguatoxin and its congeners,⁴ we have recently developed a new strategy for convergent synthesis of the polyether framework based on Suzuki cross-coupling of alkylboranes with cyclic ketene acetal triflates^{4f} and phosphates.⁴ⁱ In these previous reports we utilized only six-membered rings as the alkylborane coupling partners. The use of medium-sized alkylboranes will pave the way for a general entry to the convergent assembly of polyether natural products. In this communication, we describe a convergent and stereoselective synthesis of the HIJK ring model **1** of ciguatoxins via cross-coupling of a seven-membered alkylborane with an eight-membered ketene acetal phosphate.

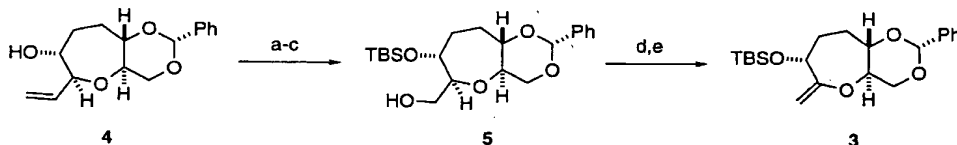
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Tetracyclic ether **1** was chosen as an appropriate target to model the synthesis of the HIJK ring system of ciguatoxins. We envisioned that compound **1** could be prepared from ketene acetal phosphate **2** and alkylborane derived from *exo*-olefin **3** (Scheme 1).



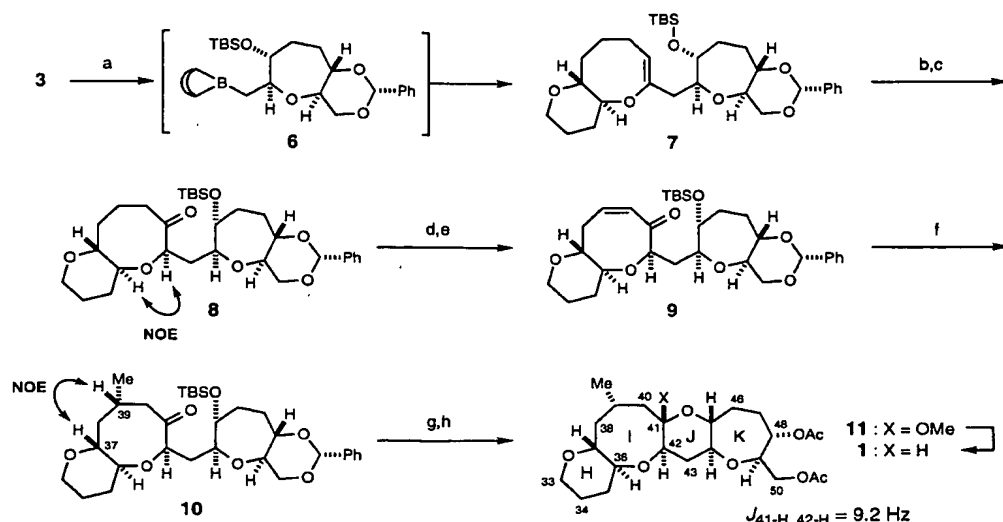
Ketene acetal phosphate **2** was prepared from the corresponding lactone⁵ following the procedure of Nicolaou et al.⁶ Synthesis of seven-membered *exo*-olefin **3** began with the known alcohol **4**⁷ (Scheme 2). Protection of **4** as its TBS ether and oxidative cleavage of the double bond followed by NaBH₄ reduction of the resultant aldehyde provided alcohol **5**. Iodination of **5** followed by treatment with KO^{*t*}-Bu afforded **3**.



Scheme 2. Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 73%; (b) OsO₄, NMO, acetone:H₂O (4:1), rt, then NaIO₄, rt; (c) NaBH₄, MeOH, 0°C, 95% (two steps); (d) I₂, Ph₃P, imidazole, benzene, rt; (e) KO^{*t*}-Bu, THF, 0°C, 96% (two steps)

Hydroboration of seven-membered *exo*-olefin **3** with 9-BBN (2.6 equiv., THF) proceeded stereoselectively to give the corresponding 9-alkyl-9-BBN **6**,⁸ which was sequentially treated with 1 M aqueous NaHCO₃ (3 equiv.), ketene acetal phosphate **2** (2 equiv.), and Pd(PPh₃)₄ (0.1 equiv.) in DMF at 50°C for 20 h to provide cross-coupled product **7** in 86% yield. Stereoselective hydroboration of **7** using thexylborane followed by oxidative workup and further oxidation of the resulting alcohol with TPAP/NMO⁹ gave ketone **8**. The stereochemistry of **8** was determined by NOE experiments.

The C39 methyl group¹⁰ was then installed by 1,4-addition of Me₂CuLi to enone **9** (Scheme 3). Thus, ketone **8** was converted to enone **9** using the Ito-Saegusa protocol.¹¹ Reaction of **9** with Me₂CuLi proceeded in a stereoselective manner to give the desired methylated product **10**. The stereochemistry of the methyl group was confirmed by a prominent NOE between 37-H and 39-H. Treatment of **10** with camphorsulfonic acid (CSA) in MeOH effected removal of the silyl and benzyldiene acetal groups and concomitant methyl acetal formation giving a dihydroxy methyl acetal, which was protected as its diacetate **11**. Finally, treatment of **11** with Et₃SiH·BF₃·OEt₂ led to the desired HIJK ring model **1** as a single stereoisomer in 90% yield.¹²



Scheme 3. Reagents and conditions: (a) 9-BBN, THF, rt, then 1 M NaHCO₃, 2, Pd(PPh₃)₄, DMF, 50°C, 86%; (b) hexylborane, THF, 0°C, H₂O₂, NaOH, rt, 75%; (c) TPAP, NMO, 4 Å MS, CH₂Cl₂, rt, quant.; (d) LiHMDS, TMSCl, Et₃N, THF, -78°C; (e) Pd(OAc)₂, CH₃CN, 60°C, 77% (two steps); (f) Me₂CuLi, Et₂O, -20°C, 71%; (g) *p*-TsOH, MeOH, rt, 98%; (h) Ac₂O, DMAP, CH₂Cl₂, 0°C, 97%; (i) Et₃SiH-BF₃·OEt₂, CH₂Cl₂-CH₃CN (1:1), 0°C, 90%

In conclusion, the described synthesis demonstrated the potential of the Suzuki cross-coupling protocol for a general entry to the convergent synthesis of polyether compounds. Further studies toward the total synthesis of ciguatoxins and related natural products based on the present strategy are currently underway and will be reported in due course.

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